

Remarks/Arguments:

In response to the Office Action dated April 17, 2006, Applicants amend claims 1, 7 and 10, cancel claim 15 without prejudice. In addition, Applicants amend the specification by deleting the definitions of "Alkyl" and "Alkylene," which were deemed to be repugnant to the usual meaning of these terms.

Claim 1 is amended to correct a grammatical error. Claim 7 is rewritten into an independent claim. Claim 10 is amended to remove two species, which are not represented by the compound of formula (I).

Objection to Claim 10

Applicants respectfully request Examiner to withdraw this objection because Applicants amended claim 10 by removing species from the claim that are not represented by the compound of formula (I).

35 USC 112, Second Paragraph Issues

In the Office Action, claim 15 was rejected under 35 USC 112, second paragraph, as being indefinite for including the term "functional." Even though Applicants respectfully disagree with this rejection, to expedite the prosecution of this application, Applicants hereby cancel claim 15. Withdrawal of this rejection is respectfully requested.

In the Office Action, claims 1, 2, 3, 4, 6, 8, 18-21 were rejected under 35 USC 112, second paragraph as being indefinite because the definition of "alkyl" in Applicants' specification was deemed to be repugnant to the usual meaning of that term. Even though Applicants respectfully disagree with this rejection, to expedite the prosecution of this application, Applicant hereby delete the "alkyl" definition from the specification and adopt the usual meaning of this term. Withdrawal of this rejection is respectfully requested.

35 U.S.C 112, First Paragraph Issues

Claim 15 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Even though Applicants respectfully disagree with this rejection, to expedite the prosecution of this application, Applicants hereby cancel claim 15. Withdrawal of this portion of the rejection is respectfully requested.

Claim 16 was rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully traverse this rejection for the following reasons.

The correlation between anxiety treatment and delta opioid receptors is well established. It is known delta opioid receptor agonists are effective in treating a variety of anxiety. For example, in year 2000 (before the filing of the instant application), Filliol et al reported the correlation between delta opioid receptors and anxiolytic condition. For example, Filliol et al found:

Together, these findings support the notion that tonic activation of δ -receptors by endogenous preproenkephalin-derived peptides positively modulates anxiety states.

Filliol, D. et al, Mice Deficient for δ - and μ -opioid receptors exhibit opposing alternations of emotional responses, Nature Genetics, Vol. 25, page 195-200 at page 196, 2000.

Filliol et al further concluded:

Therefore, in addition to their potential analgesic activity, δ -agonists may be useful in improving emotional states and, more generally, may be considered in the future as an alternative therapy to alleviate affective disorders.

Id. at 198.

Therefore, Applicants respectfully submit that, in view of the state of art when Applicant filed the application, the instant application enables a skilled person to perform the invention as claimed by 16. Withdrawal of the rejection is thus respectfully requested.

Obviousness Rejection

Claims 1, 8, 9 10, 13, 14 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al, WO 93/15062[sic]. Applicant respectfully traverses this rejection for the following reasons.

Claims 1, 8, 9, 10, 13, 14 and 20 are patentable over Chang et al because the definition of "alkyl" no longer includes unsaturated hydrocarbyl.

In the Office Action rejection, Examiner relied on Example 110 of Chang et al, which contains an allyl group at the bottom of the structure. Because the amendment to the specification changes the scope of claims 1, 8, 9, 10, 13, 14 and 20, the claims now have the additional difference of not having an alkenyl group at the bottom and are thus unobvious in view of Chang et al. Withdrawal of this rejection is respectfully requested.

Claims 1, 8, 9, 10, 13, 14 and 20 are patentable over Chang et al because Chang et al teaches away from the instant claims.

A prior art that teaches away from claimed invention is a significant factor to be considered in determining obviousness.

In this case, Chang et al. teaches that it is important to have the substitution on the piperazine ring to achieve the desired property. See page 60 of the comments made during a response by Chang et al. on February 9, 1996 (a rule 132 declaration filed by Chang et al.) during the prosecution of Chang et al.'s U.S. patent application, copies of the relevant pages were attached herewith as Appendix I. In Chang et al.'s response, Chang et al. made the following statements:

Specially, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, *show a general trend in which the substituted compounds have significantly greater opioid activity.* (Emphasis added).

A patent application's prosecution history is generally considered as an integrated part of the patent. A person skilled person reading Chang et al. as a whole would be motivated to modify Chang et al. reference in such a way that it would not arrive at the present invention because the skilled person would retain the methyl groups on the piperazine ring as specifically taught by Chang et al. Therefore, the motivation to modify Chang et al. to arrive at the present invention is lacking for this reason and claims 1, 8, 9, 10, 13, 14 and 20 are unobvious over Chang et al. reference for this reason.

In addition, a prior art reference must be considered in its entirety, including disclosures that teach away from the claims.

A person reading Chang et al. as a whole will be led to believe that to achieve an optimal delta receptor binding activity, the central piperazine ring must be substituted, and thus, would not be motivated to modify Chang et al. to arrive at the present invention, which contains no substitution on the piperazine ring. In numerous occasions, Chang et al. teaches that the preferred compounds (See bottom of page 10 of Chang et al.) of Chang et al. to bind delta opioid receptors requires at least one of R3, R4 and R5 to be methyl (see also Page 11, line 15; Page 32, lines 16-17; Page 34, lines 7-8; Page 36, lines 3-4; Page 38, lines 2-3; and Page 39, lines 7-8). In addition, Chang et al. disclosed 92 working examples of compounds (see Examples 1-92) that were believed to be effective in binding delta receptors. However, all these compounds contain one or more methyl groups on their piperazine rings. It would be reasonable

for a person of ordinary skill to believe that the one or more methyl groups on the piperazine rings are critical in achieving the desirable delta receptor binding activity. In contrast, compounds of the instant claims do not contain any methyl on the piperazine ring. Therefore, an ordinary skilled person reading Chang et al would not be motivated to modify Chang et al. to arrive at the present invention and the instant claims are not obvious in view of Chang et al. for this additional reason.

In conclusion, an ordinary skilled person in the art reading Chang et al as a whole would not be motivated to modify Chang in such a way to arrive at the instant invention. Therefore, Claims 1, 8, 9, 10, 13, 14 and 20 are patentable over Chang et al for this additional reason and withdrawal of the rejection is respectfully requested.

Applicants believe the application is in condition for allowance, which action is respectfully requested.

Other Issues

Even though it is the Examiner's prerogative to require Applicants to respond to an Office Action on merit in 30 days, it is a common practice for an Examiner to set a three months responding period. Applicants would want to point out to the Examiner that a shorten period of 30 days was required for responding to the instant Office Action. In any case, a petition for a 3 month extension of time is filed herewith, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 26-0166, referencing Attorney Docket No. 100884-1P US.

The Commissioner is hereby authorized to charge \$200 for excess claim fees. Please charge any deficiency in the fees or credit any overpayment to deposit account No. 26-0166, referencing Attorney Docket No. 100884-1P US.

Respectfully submitted,

/Jianzhong SHEN, Reg.#48076/

Name: Jianzhong Shen
Dated: Aug. 8, 2006
Reg. No.: 48076
Phone No.: 302-886-8854
Global Intellectual Property, Patents,
AstraZeneca,
1800 Concord Pike,
Wilmington,
DE-19850-5437



Appendix I

Patent Application
3022-107

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: "OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature
MARY B. CARUSO
Name of Person Mailing This Paper
FEBRUARY 9, 1996
Date of Mailing
E65612449305
Express Mail Label Number

AMENDMENT RESPONDING TO AUGUST 9, 1995 OFFICE ACTION IN U.S. PATENT APPLICATION NO. 08/284,445

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the 9 August 1995 Office Action in the above-identified application,
please amend the application, as follows:

In the Claims

Amend the claims as follows:

B

Appendix I - Continued

Patent Application
3022-107

The Examiner has requested the month of publication for references BD-BH, which are as follows. BD: November, 1993; BE: October, 1993; BF: November, 1993; BG: November, 1993; BH: November, 1993.

Claims 1-8, 12-14, 38-40 and 44 were rejected in the 9 August 1995 Office Action as being drawn to improper Markush group(s) on the basis that the variables G, R⁹ and R¹⁰ embrace more than one invention as discussed in the restriction requirement.

In the restriction requirement dated April 5, 1995, the Examiner sought to limit claim 1 to G=N and exclude R⁹ and R¹⁰ from being C₃ and higher. Applicants respectfully disagree with this suggestion, particularly since the claims have already been examined on the merits. Furthermore, according to M.P.E.P. Section 803,

"[i]f the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to distinct or independent inventions."

Thus, since examination on the merits has already occurred, it is clear that the Markush groups of the claims are in proper form according to the M.P.E.P.

For the foregoing reasons, the Section 112 rejections have been overcome, as described in the above discussion, and through the foregoing amendments, which serve to clarify claims 1, 5, 7, 12, 14-17, 38 and 44.

Arguments for Patentability

only G=N
new arguments
made in the
restriction
requirement
to overcome
the MPEP
section 803
rejection

Appendix I - Continued

Patent Application
3022-107

As discussed above, references AM, AS-AU and BD-BH do not qualify as prior art.

Claims 1, 3, 14-17 and 38-40 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 102(b) over references AW and AY. Furthermore, claims 20, 21 and 24 were rejected in the 9 August 1995 Office Action under 35 U.S.C. Section 103 over references AW and AY.

AW and AY are directed to a calcium antagonist, KB-2796, which is I-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride. Related compounds A, B, C, Flunarazine and Cinnarizine are also discussed. (See the structural configurations in AW, Figure 1 and AY, Table 1.) None of the compounds discussed in AW or AY teach or suggest the compounds of the present invention.

Instead, the present invention, as claimed, is related to opioid diarylmethylpiperazines and piperidines. The claims of the present invention, as amended, are directed to diarylmethylpiperazines and piperidines having a particular type of substituent attached to at least one of the carbon atoms in the piperazine ring. For example, according to claim 1, as amended, the substituents on the piperazine are as follows:

"R³, R⁴ and R⁵ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R³, R⁴ or R⁵ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R³, R⁴ and R⁵ together may form a bridge of 1 to 3 carbon atoms."

Argument

Appendix I - Continued

Patent Application
3022-107

In contrast, AW and AY do not teach or suggest such compounds having a substituent attached to at least one of the carbon atoms in the piperazine ring.

132?
According to the enclosed Declaration under 37 C.F.R. 1.131 by Dr. Robert McNutt, comparisons have been made between compounds that have a substituent attached to at least one of the carbon atoms in the piperazine ring and those that do not, using the assay procedures set out in Example 92 on pages 156-157 of the specification.

Specifically, these tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II, had no substituents on carbon atoms of the piperazine ring. The other compound of the pair was the same as the first, except that it had two methyl groups on carbon atoms of the piperazine ring. The test results, comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity.

The compounds tested were as follows, wherein Compounds 1-4 have no substituents on carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on carbon atoms of the piperazine ring:

Compound 1: (\pm) -3-(-(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (\pm) -3-((1R*)-(-(2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (\pm) -3-(-(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Appendix I - Continued

Patent Application
3022-107

Compound 2a: (+)-3-((1R*)-1-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (+)-3-((1-((4-Allyl-1-piperazinyl)benzyl)phenol);

Compound 3a: (+)-3-((1R*)-1-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (+)-3-((1-((4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (+)-3-((1R*)-1-((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

The compounds having methyl groups on the piperazine ring can be found in the present specification as follows. Compound 1a can be found, for example, on page 12, number 1. Compound 2a can be found, for example, on page 14, number 40. Compound 3a can be found, for example, on page 15, number 47. Compound 4a can be found, for example, on page 21, number 136.

The test results for Compounds 1-4 and Compound 1a-4a using assays described in Example 92 on pages 156-157 of the specification are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

Appendix I - Continued

Patent Application
3022-107

nd = not determined

* Test results showed that Compound 2 has antagonist activity rather than agonist activity in the mouse vas deferens assay

According to Dr. McNutt's Declaration, the test results show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

Thus, the test results comparing compounds in which the piperazine ring is substituted with two methyl groups, with those that do not have a substituent on any of the carbon atoms of the piperazine ring, show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification. This general trend was an unexpected result of the addition of a substituent on the piperazine ring, which is not taught or suggested by the calcium antagonists disclosed in references AW or AY, taken alone or in combination.

Appendix I - Continued

Patent Application
3022-107

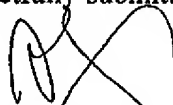
Thus, references AW and AY do not teach or suggest the compounds of the present invention, as claimed, which is directed to opioid diarylmethylpiperazines and piperidines in which there is a substituent attached to at least one of the carbon atoms in the piperazine ring.

Applicants note for the record that claims 4-8, 12, 13, 18, 19, 23, 25-28, 44, 64 and 65 have been found patentable over the prior art, particularly since AS-AU, BD-BH and AM do not qualify as prior art as discussed above.

For all of the foregoing reasons, claims 1, 3-8, 12-21, 23-28, 38-40, 44, 64 and 65, as amended, are fully patentably distinguished over the references cited and are in condition for allowance.

If any issues remain outstanding in connection with the allowance of this application, the Examiner is requested to contact the undersigned attorney, at (919) 990-9531 to discuss their resolution, so that this application can be passed to issue at an early date, consistent with the substantial advance in the art achieved by the invention claimed in this application.

Respectfully submitted,



Steven J. Hultquist
Registration No. 28,021
Attorney for Applicants

INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
P. O. Box 14329
Research Triangle Park, NC 27709
Phone: (919) 990-9531
Fax: (919) 990-9532
Attorney File: 3022-107

Appendix I - Continued



Patent Application
3022-107

#10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Kwen-Jen CHANG, et al.

Group Art Unit: 1202

Application No. 08/284,445

Examiner: E. Bernhardt

Date Filed: August 3, 1994

For: "OPIOID DIARYLMETHYLPIPERAZINES AND PIPERIDINES"

EXPRESS MAIL CERTIFICATE

It hereby is certified by the person identified below that this paper is being mailed by such person to the Commissioner of Patents and Trademarks on the date specified, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231, and Express Mailed under the provisions of 37 CFR 1.10.

Mary B. Caruso
Signature
MARY B. CARUSO
Name of Person Mailing This Paper
FEBRUARY 9, 1996
Date of Mailing
EG561244813US
Express Mail Label Number

DECLARATION OF DR. ROBERT MCNUTT UNDER 37 C.F.R. Section 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Robert Walton McNutt, Jr., hereby declare and state the following:

1. I am a citizen of the United States of America, residing at 700 Morreene Road, Durham, NC 27705, and hold a Ph.D. in organic chemistry from Boston College, granted in 1977, and I have been employed by Burroughs Wellcome, now Glaxo Wellcome, since 1979 and continuing to date, currently holding the position of Research Scientist in such company.

Appendix I - Continued

Patent Application
3022-107

2. I am an inventor of subject matter described and claimed in United States Patent Application Serial No. 08/284,445 filed 03 August 1994 in the names of Kwen-Jen Chang, Grady Evan Boswell, Dulce Garrido Bubacz, Mark Allan Collins, Ann Otstot Davis, and Robert Walton McNutt, Jr. (and hereinafter referred to as the "Application").

3. I am aware that the United States Patent and Trademark Office has issued an Office Action dated 09 August 1995 in the Application, and that in such Office Action, among other rejections, claims 1, 3, 14-17 and 38-40 were rejected under 35 U.S.C. Section 102(b) as anticipated by references AW and AY, and claims 20, 21 and 24 were rejected as obvious in view of references AW and AY. References AW and AY are as follows:

AW Iwamoto et al., "Calcium Antagonism by KB-2796, a New Diphenylpiperazine Analogue, in Dog Vascular Smooth Muscle," J. Pharm. Pharmacol. 43, 535-539, 1991 ("Iwamoto I"); and

AY Iwamoto et al., "Effects of KB-2796, a New Calcium Antagonist, and Other Diphenylpiperazines on [3H]Nitrendipine Binding," J. Pharmacol., 48, 241-247 (1988) ("Iwamoto II").

4. I have read and am familiar with the references identified in Paragraph 3 above.

5. The references identified in Paragraph 3 above disclose the following compounds:

"Compound A": 3-(4-chloro- α -(4-(3-methylbenzyl)piperazinyl)benzyl)phenol;

"Compound B": 1-(bis(4-methoxyphenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

"Compound C": 1-(bis(4-fluorophenyl)methyl)-4-(3-(2,3,4-trimethoxyphenyl)-2-propen-1-yl)piperazine;

KB-2796: 1-bis(4-fluorophenyl)methyl)-4-(2,3,4-trimethoxybenzyl)piperazine;

Appendix I - Continued

Patent Application
3022-107

Flumarizine: 1-(bis(4-fluorophenyl)methyl)-4-(3-phenyl-2-propen-1-yl)piperazine; and

Cinnarizine: 1-(diphenylmethyl)-4-(3-phenyl-2-propen-1-yl)piperazine.

6. None of the compounds disclosed in Iwamoto I or II, as identified in Paragraph 5 above, have any substituents attached to any of the carbon atoms in the piperazine ring.

7. I have collaborated on tests conducted on certain diphenylpiperazine compounds using the assay procedures set out in Example 92 on pages 156-157 of the specification of the Application. These tests included four pairs of compounds, in which one of the two compounds, like all of the compounds disclosed in Iwamoto I and II and identified in Paragraph 5 above, had no substituents on the carbon atoms of the piperazine ring. The other compound of the pair was the same as the first except that it had two methyl groups on the carbon atoms of the piperazine ring.

8. The compounds tested according to Paragraph 7 were as follows, wherein Compounds 1-4 have no substituents on the carbon atoms of the piperazine ring, and Compounds 1a-4a have two methyl groups on the carbon atoms of the piperazine ring:

Compound 1: (\pm)-3-(α -(4-Allyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 1a: (\pm)-3-((αR^*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-chlorobenzyl)phenol;

Compound 2: (\pm)-3-(α -(4-Allyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 2a: (\pm)-3-((αR^*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-bromobenzyl)phenol;

Compound 3: (\pm)-3-(α -(4-Allyl-1-piperazinyl)benzyl)phenol;

Appendix I - Continued

Patent Application
3022-107

Compound 3a: (\pm)-3-((α R*)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

Compound 4: (\pm)-3-(α -(4-Methyl-1-piperazinyl)benzyl)phenol; and

Compound 4a: (\pm)-3-((α R*)- α -((2R*,5S*)-2,4,5-Trimethyl-1-piperazinyl)benzyl)phenol.

9. The test results for Compounds 1-4 and Compound 1a-4a described in Paragraphs 7-8, using assays described in Example 92 on pages 156-157 of the specification of the Application, are as follows:

Compound	Mu Receptor IC50 (nM)	Mouse Vas Deferens ED50 (nM)	Delta Receptor IC50 (nM)
Compound 1	3500	2000	50
Compound 1a	90	40	15
Compound 2	2000	*	60
Compound 2a	200	100	80
Compound 3	200	nd	60
Compound 3a	25	78	1.3
Compound 4	700	nd	140
Compound 4a	1.6	46	38

nd = not determined

*Test results showed that Compound 2 has antagonistic activity rather than agonist activity in the mouse vas deferens assay

10. The test results listed in Paragraph 9 above show that substituted Compound 1a has fifty times more potency than unsubstituted Compound 1 according to the Mouse Vas Deferens ED50, more than thirty times more potency according to the Mu Receptor IC50, and more than three times more potency according to the Delta Receptor IC50. Substituted Compound 2a has ten times more potency than Compound 2 according to the Mu Receptor IC50. Substituted Compound 3a has more than 45 times more potency than unsubstituted Compound 3 according to the Delta Receptor IC50 and 8 times more potency according to the Mu Receptor IC50. Compound 4a has more than four hundred

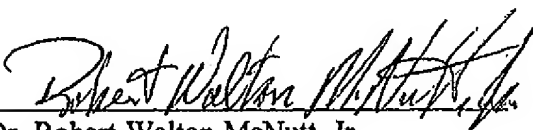
Appendix I - Continued

Patent Application
3022-107

times more potency than unsubstituted Compound 4 according to the Mu Receptor IC50 and more than three times more potency according to the Delta Receptor IC50.

11. The test results in Paragraphs 9 and 10 above comparing compounds in which the piperazine ring is substituted with two methyl groups on the carbon atoms with those that do not have a substituent on any of the carbon atoms of the piperazine ring show a general trend in which the substituted compounds have significantly greater opioid activity according to test results of assays described in Example 92 on pages 156-157 of the specification of the Application.

All statements made herein of my own knowledge are true, and all statements made on inference and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.


Dr. Robert Walton McNutt, Jr.

Date: February 7, 1996